

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Confirmation No.: 7412
Serial No. 10/539,234	Art Unit: 1616
Shirou Maeda et al.	Examiner: Nathan W. Schlientz
Filed: July 15, 2005	

DECLARATION (2) UNDER 37 CFR 1.132

Honorable Commissioner of Patents and Trademarks

Sir,

I, Shirou Maeda declare that:

I am a citizen of Japan and a resident of Nagaokakyo-shi, Kyoto Prefecture, Japan;

I graduated from a graduate school, Master's Course Faculty of Science, The Osaka City University, Japan in 1967;

I received the Doctor degree on the study of "Studies on the Synthesis of Bioactive Lignans by Oxidative Coupling Reaction" from The Osaka City University, Japan in 1995;

I have been an employee of Hamari Chemicals, Ltd. Japan, since October of 2000 up to this time;

I have been engaged in research at Core Technology Laboratory;

I am one of inventors of the above-identified patent application;

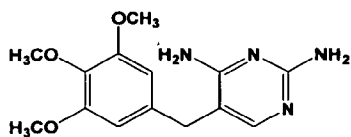
The experiments set out below were conducted under my supervision and direction.

## EXPERIMENT

### Experiment 1 Preparation of test compounds

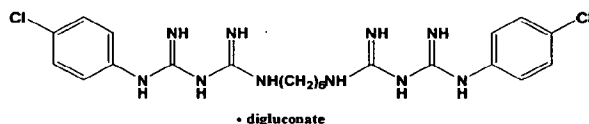
#### I. Comparative compounds

##### (A) Trimethoprim



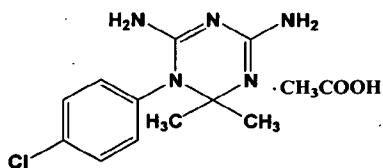
Trimethoprim (GlaxoSmithKline, USA) was purchased on the market and used for the test.

##### (B) Chlorhexidine digluconate



Chlorhexidine digluconate (Wako Pure Chemical Industries, Japan) was purchased on the market and used for the test.

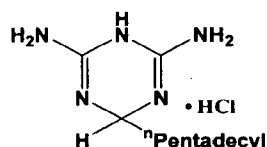
##### (C) 2,4-Diamino-3,6-dihydro-6,6-dimethyl-1-(4'-chlorophenyl)-1,3,5-triazine acetate



—Compound No. 1 described at Table II on page 240 of Journal of the Medicinal Chemistry 1977, vol.20 (No.2) —

This compound was prepared according to the method described in the Journal.

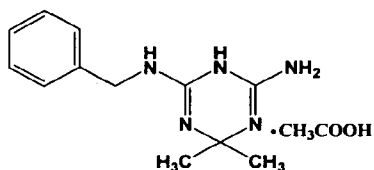
##### (D) 2,4-Diamino-3,6-dihydro-6-n-pentadecyl-1,3,5-triazine hydrochloride



To 1.0 g (4.16 mmol) of hexadecanal were added 30 ml of ethanol, 3.97 g (41.6 mmol) of guanidine hydrochloride and 2.87 g (20.8 mmol) of potassium carbonate, and the mixture was refluxed for 17 hours. After removal of the solvent by evaporation under reduced pressure, water and ethyl acetate was added to the residue, and the resulting precipitated insoluble materials were obtained by filtration. The thus-obtained insoluble materials were suspended to methyl alcohol, followed by adding concentrated hydrochloric acid dropwise to make a uniform solution. The solvent was distilled off under reduced pressure. The residue was dissolved in a small amount of methyl alcohol, followed by adding water dropwise to obtain 0.5 g of pale gray crystals melting at 145-148°C.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 0.85 (3H, t,  $J=6.6$  Hz), 1.04-1.51 (27H, m), 2.28 (1H, t,  $J=7.4$  Hz), 4.68 (0.5H, brt-like), 7.00-7.40 (2H, br), 8.25 (1H, brs).

(E) 4-Amino-3,6-dihydro-6,6-dimethyl-2-benzylamino-1,3,5-triazine acetate



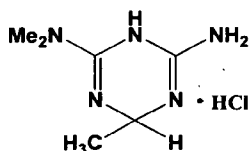
140 ml of n-propyl alcohol were added to 30 g (0.21 mol) of benzylamine hydrochloride and 18.4 g (0.22 mol) of dicyanodiamide, and the mixture was refluxed for 15 hours, and

cooled to the room temperature. The precipitating crystals were obtained by filtration. Recrystallization from n-propyl alcohol gave 31 g of colorless crystals.

264 ml of ethyl alcohol, 104 ml of acetone and 10 ml of concentrated hydrochloric acid were added to 24 g (0.11 mol) of thus-obtained crystals and the mixture was refluxed for 48 hours. After removal of the solvent by evaporation under reduced pressure, the residue was dissolved in 150 ml of ethyl alcohol, followed by adding 100 ml of water and 18 ml of 5 N sodium hydroxide solution. The mixture was refluxed for 1 hour, and then concentrated under reduced pressure. The concentrate was extracted with chloroform, and the extract was washed with water and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution with a mixture of chloroform, methyl alcohol and acetic acid (8:2:1) to give 1.5 g of colorless crystals melting at 114-118°C.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : .36 (6H, s,  $\text{CH}_3 \times 2$ ), 1.91 (3H, s,  $\text{CH}_3\text{COO}^-$ ), 4.46 (2H, s,  $\text{ArCH}_3\text{NH}$ ), 7.2-7.4 (6H, m,  $\text{ArH}$  and  $\text{NH}$ ), 8.53, 9.27, 9.71 (each H, m,  $\text{NH}$  and  $\text{NH}^+$ ).

(F) 4-Amino-3,6-dihydro-6-methyl-2-dimethylamino-  
1,3,5-triazine hydrochloride



-Compound 18 at Table II on columns 11-12 of US 7,034,021B2

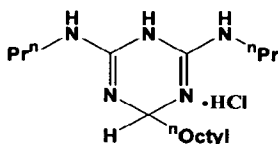
The compound was prepared according to the method described in Example describing the preparation of compound 18 of US 7,034,021B2.

Colorless crystals

mp. 228-229°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  : 1.32 (3H, d,  $J=6\text{Hz}$ ,  $\text{CH}_3\text{CH}$ ), 3.03 (6H, s,  $\text{CH}_3\text{NCH}_3$ ), 4.81 (H, d,  $J=6\text{Hz}$ ,  $\text{CH}_3\text{CH}$ ), 7.1-7.6 (2H, m,  $\text{NH}_2$ ), 8.36, 8.54 (each H, m,  $\text{NH}$  and  $\text{NH}^+$ ).

(G) 2,4-Di-(n-propylamino)-3,6-dihydro-6-n-octyl-1,3,5-triazine hydrochloride

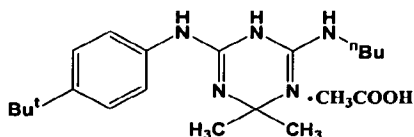


300 ml of ethyl alcohol, 7.1 g (49.6 mmol) of 1-nonanal and 2.0 ml of concentrated hydrochloric acid were added to 10.0 g (45.1 mmol) of  $\text{N}^1, \text{N}^5$ -dipropylbiguanide hydrochloride prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 24 hours and then was evaporated under reduced pressure.

Recrystallization from methyl ethyl ketone gave 1.5 g of colorless crystals melting at 66-70°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 0.8-1.0 (9H, m,  $\text{CH}_3 \times 3$ ), 1.1-1.8 (18H, m,  $(\text{CH}_2)_7$  and  $\text{NHCH}_2\text{CH}_2\text{CH}_3 \times 2$ ), 3.31 (4H, dt-like,  $\text{NHCH}_2\text{CH}_2\text{CH}_3 \times 2$ ), 4.62 (H, t,  $J=6\text{Hz}$ ,  $\text{HCCH}_2$ ), 7.42 (2H, t,  $J=5\text{Hz}$ ,  $\text{NHCH}_2\text{CH}_2\text{CH}_3 \times 2$ ), 8.23 (each H, m,  $\text{NH}$  and  $\text{NH}^+$ ).

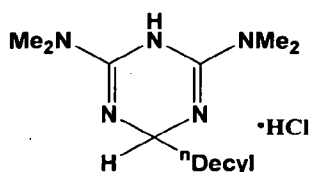
(H) 2-(4-t-Buthylphenylamino)-4-n-buthylamino-3,6-dihydro-6,6-dimethyl-1,3,5-triazine acetate



240 ml of methyl alcohol, 120 ml of acetone and 2.5 ml of concentrated hydrochloric acid were added to 12.0 g (36.8 mmol) of N<sup>1</sup>-octyl-N<sup>5</sup>-(4-tert-butylphenyl)biguanide hydrochloride prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 40 hours. 13.0 ml of 5N sodium hydroxide solution was added to the mixture, and the mixture was evaporated under reduced pressure. The residue was dissolved in 160 ml of ethyl alcohol, followed by adding 106 ml of water and 11.0 ml of 5N sodium hydroxide solution. The mixture was refluxed for 2 hours, and concentrated under reduced pressure. The concentrate was extracted with ethyl acetate, and the extract was washed with water, and evaporated under reduced pressure. Recrystallization of the residue from methyl ethyl ketone gave 11.3 g of colorless crystals melting at 164-166°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 0.90 (3H, t, J=7Hz, CH<sub>3</sub>), 1.2-1.6 (19H, m, (CH<sub>2</sub>)<sub>2</sub> and (CH<sub>3</sub>)<sub>5</sub>), 2.03 (3H, s, CH<sub>3</sub>COO<sup>-</sup>), 3.32 (2H, dt-like, NHCH<sub>2</sub>), 7.26 (2H, d, J=9Hz, ArH), 7.48 (2H, d, J=9Hz, ArH), 8.30, 9.31, 9.47, 10.51 (each H, m, NH and NH<sup>+</sup>).

(I) 2,4-Di-(dimethylamino)-3,6-dihydro-6-n-decyl-1,3,5-triazine hydrochloride



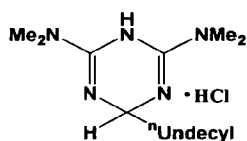
200 ml of ethyl alcohol, 6.0 g (35.2 mmol) of 1-undecanal and 1.6 ml of concentrated hydrochloric acid were added to 6.1

g (31.3 mmol) of N<sup>1</sup>,N<sup>5</sup>-tetramethylbiguanide hydrochloride prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 48 hours and then evaporated under reduced pressure.

Recrystallization of the residue from methyl ethyl ketone gave 6.9 g of colorless crystals melting at 97-99°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 0.88 (3H, t, J=6Hz, CH<sub>3</sub>), 1.1-1.4 (16H, m, (CH<sub>2</sub>)<sub>8</sub>), 1.65 (2H, m, HCCH<sub>2</sub>), 3.14 (12H, s, CH<sub>3</sub>×4), 4.92 (H, t, J=6Hz, HCCH<sub>2</sub>), 9.14, 9.17 (NH and NH<sup>+</sup>).

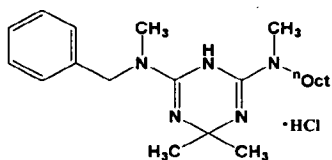
(J) 2,4-di-(dimethylamino)-3,6-dihydro-6-undecyl-6-dimethyl-1,3,5-triazine hydrochloride



200 ml of ethyl alcohol, 6.3 g (34.1 mmol) of 1-dodecanal and 1.6 ml of concentrated hydrochloric acid were added to 6.0 g (31.0 mmol) of N<sup>1</sup>,N<sup>5</sup>-tetramethylbiguanide hydrochloride that was prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 24 hours and then evaporated under reduced pressure. Recrystallization of the residue from acetonitrile gave 6.0 g of colorless crystals melting at 98-100°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ : 0.82 (3H, t, J=6Hz, CH<sub>3</sub>), 1.2-1.4 (18H, m, (CH<sub>2</sub>)<sub>9</sub>), 1.57 (2H, m, HCCH<sub>2</sub>), 3.03 (12H, s, CH<sub>3</sub>×4), 4.63 (H, t, J=6Hz, HCCH<sub>2</sub>), 8.56 (NH and NH<sup>+</sup>)

(K) 4-(Octyl(methyl)amino)-3,6-dihydro-6,6-dimethyl-2-(benzyl(methyl)amino)-1,3,5-triazine hydrochloride



180 ml of ethyl alcohol, 45 ml of acetone and 0.8 ml of concentrated hydrochloric acid were added to 13.0 g (32.1 mmol) of N<sup>1</sup>-octyl-N<sup>1</sup>-methyl-N<sup>5</sup>-benzyl-N<sup>5</sup>-methyl-biguanide hydrochloride prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 48 hours, and evaporated under reduced pressure. The residue was dissolved in 120 ml of ethyl alcohol, followed by adding 75 ml of water and 15.3 ml of 5N sodium hydroxide solution. The mixture was refluxed for 2 hours, and concentrated under reduced pressure. The concentrate was extracted with toluene, and the extract was washed with water, and evaporated under reduced pressure. To the residue were added 16 ml of a mixed solution of 4N hydrochloric acid and ethyl acetate, and the mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution with a mixed solution of chloroform, methyl alcohol and acetic acid (8:1.5:1) to give 4.6 g of pale-yellow semisolid products.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 0.85 (3H, t, J=6Hz, CH<sub>3</sub>), 1.1-1.6 (12H, m, (CH<sub>2</sub>)<sub>6</sub>), 1.84 (6H, s, CH<sub>3</sub>×2), 3.16, 3.20 (each 3H, s, NCH<sub>3</sub>×2), 3.41 (2H, m, CH<sub>3</sub>NCH<sub>2</sub>), 4.74 (2H, s, ArCH<sub>2</sub>NCH<sub>3</sub>), 7.1-7.3 (6H, m, ArH and NH), 8.32, 8.51 (each H, m, NH and NH<sup>+</sup>)

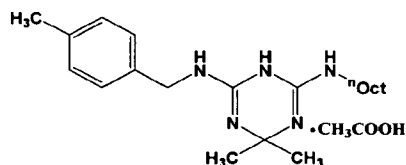
## II. Compounds of the present invention

### Compound No. (9)

4-Octylamino-3,6-dihydro-6,6-dimethyl-2-(4'-methylbenzyl-



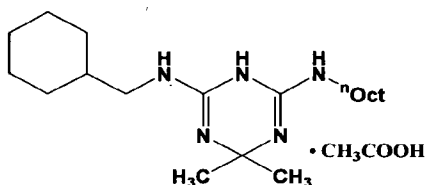
amino)-1,3,5-triazine acetate (Example 58 in the specification)



This compound was prepared according to the method described on Example 58 in the present specification.

Compound No. (10)

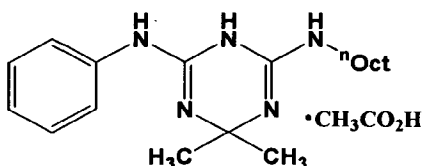
4-Octylamino-2-cyclohexylmethylamino-3,6-dihydro-6,6-dimethyl-1,3,5-triazine acetate (Example 65 in the specification)



This compound was prepared according to the method described on Example 65 in the present specification.

Compound No. (12)

4-Octylamino-3,6-dihydro-6,6-dimethyl-2-phenylamino-1,3,5-triazine acetate



100 ml of methyl alcohol, 80 ml of acetone and 0.6 ml of concentrated hydrochloric acid were added to 8.2 g (22.6 mmol)

of N<sup>1</sup>-phenyl-N<sup>5</sup>-octylbiguanide hydrochloride prepared in the similar procedure to Reference Examples 1 and 2 of the present application, and the mixture was refluxed for 20 hours, and evaporated under reduced pressure. The residue was dissolved in 100 ml of ethyl alcohol, followed by adding 65 ml of water and 9.5 ml of 5N sodium hydroxide solution. The mixture was refluxed for 1 hour, and concentrated under reduced pressure. The concentrate was extracted with ethyl acetate, and the extract was washed with water, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution with a mixed solution of chloroform, methyl alcohol and acetic acid (9:1:1) to give 5.0 g of colorless crystals melting 122-124°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.87(3H,t,J=7Hz,CH<sub>3</sub>), 1.2-1.4(10H,m), 1.43(6H,s,(CH<sub>3</sub>)<sub>2</sub>C), 1.53(2H,m,NHCH<sub>2</sub>CH<sub>2</sub>), 2.03(3H,s,CH<sub>3</sub>COO<sup>-</sup>), 3.29(2H,br dt-like,NHCH<sub>2</sub>CH<sub>2</sub>), 7.0-7.6(5H,m,ArH)

#### Experiment 2 Antibacterial activity test

Minimal inhibitory concentration (MIC) of test compounds (A) to (K), and (9), (10) and (12) was determined according to the similar procedures to those described in the specification.

Test results are shown in Table 1.

Table 1 Minimal Inhibitory Concentration (MIC)

MIC( $\mu$ g/mL)      Contact Time: 24hr				
Test Compounds	Gram(+) bacteria		Gram(-) bacteria	
	S.a. <sup>a</sup>	MRSA <sup>b</sup>	E.c. <sup>c</sup>	P.a. <sup>d</sup>
A	0.8	3.2	6.3	>100
B	0.2	3.2	1.6	50
C	>100	>100	>100	>100
D	25.0	18.8	>100	>100
E	>100	>100	>100	>100
F	>100	>100	>100	>100
G	3.1	3.1	25	>100
H	3.1	1.6	25	50
I	6.3	6.3	25	100
J	3.1	3.1	25	100
K	3.1	3.1	12.5	50
(9)	1.6	1.6	12.5	12.5
(10)	1.6	1.6	6.3	50
(12)	1.6	1.6	12.5	25

<sup>a</sup> *Staphylococcus aureus* 209PJC,

<sup>b</sup> methicillin-resistant *Staphylococcus aureus* 97-115,

<sup>c</sup> *Escherichia coli* NIHJ JC-2,

<sup>d</sup> *Pseudomonas aeruginosa* PA0-1

### Experiment 3

#### Bactericidal activity test

Bactericidal activity of test compounds (A) to (D), (F) to (K), and (9), (10) and (12) was evaluated according to the similar procedures to those described in the specification.

The contact time between a test compound and a bacterium was 5 minute and 0.5 minutes.

Test results are shown in Table 2.

Table 2 Minimal Bactericidal Concentration (MBC)

MBC( $\mu$ g/mL)					
Test Compounds	Contact time (minutes)	Gram(+) bacteria		Gram(-) bacteria	
		S.a. <sup>a</sup>	MRSA <sup>b</sup>	E.c. <sup>c</sup>	P.a. <sup>d</sup>
A	5	>100	>50	>100	>50
B	0.5	>200	>200	100	>200
C	0.5	>100	>100	>100	>100
D	0.5	>200	>200	>200	>200
F	0.5	>200	>200	>200	>200
G	0.5	>200	>200	100	100
H	0.5	200	>200	200	100
I	0.5	>200	>200	100	100
J	0.5	200	>200	50	25
K	0.5	>200	200	25	25
(9)	0.5	25	25	25	25
(10)	0.5	25	25	12.5	25
(12)	0.5	50	50	25	25

<sup>a</sup> *Staphylococcus aureus* 209PJC,

<sup>b</sup> methicillin-resistant *Staphylococcus aureus* 97-115,

<sup>c</sup> *Escherichia coli* NIHJ JC-2,

<sup>d</sup> *Pseudomonas aeruginosa* PA0-1

It is clear from Table 2 that compounds (9), (10) and (12) show much stronger bactericidal activity than compounds (A) to (D) and (F) to (K).

It is declared by the undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 2 day of June, 2009

Shiron Maeda

Shirou Maeda



LEXSEE 492 F3D 1350



Caution

As of: May 28, 2009

**TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., Plaintiffs-Appellees, v. ALPHAPHARM PTY., LTD. and GENPHARM, INC., Defendants-Appellants.**

06-1329

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169

June 28, 2007, Decided

**SUBSEQUENT HISTORY:** Later proceeding at *Takeda Chem. Indus. v. Ranbaxy Labs., Ltd.*, 2007 U.S. App. LEXIS 15883 (Fed. Cir., June 28, 2007)

US Supreme Court certiorari denied by *Alphapharm Pty v. Takeda Chem. Indus.*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008)

**PRIOR HISTORY:** [\*\*1]

Appealed from: United States District Court for the Southern District of New York Judge Denise Cote. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 2006 U.S. Dist. LEXIS 6710 (S.D.N.Y., 2006)

**DISPOSITION:** AFFIRMED.

**CASE SUMMARY:**

**PROCEDURAL POSTURE:** Defendant, the manufacturer of a generic version of pioglitazone, a compound successful in anti-diabetic treatment, appealed from a holding of the United States District Court for the Southern District of New York that the generic manufacturer failed to prove by clear and convincing evidence that the patent claims asserted by plaintiff patent holder were invalid as obvious under 35 U.S.C.S. § 103, at the time the invention was made.

**OVERVIEW:** The generic manufacturer filed an abbreviated new drug application seeking U.S. Food and Drug

Administration approval to market its generic product under 21 U.S.C.S. § 355(j) *et seq.* The district court rejected the obviousness argument, because the closest prior art compound exhibited negative properties that would have directed one of ordinary skill in the art away from the compound that was eventually patented as the lead compound for anti-diabetic treatment. The most similarly structured compounds exhibited negative side effects, while other compounds were more promising at the time of invention. The court of appeals concluded that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and that the patent had not been shown to be invalid. The trial also did not err in holding that the generic manufacturer failed to establish a *prima facie* case of obviousness. Because the district court's conclusions were not clearly erroneous and were supported by the record evidence, there was no basis to disturb them.

**OUTCOME:** The judgment of the district court was affirmed.

**LexisNexis(R) Headnotes**

**Patent Law > Nonobviousness > General Overview**

[HN1] An invention is not patentable, *inter alia*, if the differences between the subject matter sought to be pa-

tented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. 35 U.S.C.S. § 103(a).

***Patent Law > Infringement Actions > Defenses > Patent Invalidity > Validity Presumption***

[HN2] Because a patent is presumed to be valid under 35 U.S.C.S. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. Whether an invention would have been obvious under 35 U.S.C.S. § 103 is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial.

***Patent Law > Nonobviousness > Elements & Tests > Prior Art***

[HN3] The factors that control an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of nonobviousness.

***Patent Law > Nonobviousness > Elements & Tests > Prior Art***

[HN4] Structural similarity between claimed and prior art subject matter, which is proven by combining references or otherwise where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of adequate support in the prior art for the change in structure.

***Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness***

[HN5] Normally a prima facie case of obviousness is based upon structural similarity, that is, an established structural relationship between a prior art compound and the claimed compound. That is so because close or established structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.

***Patent Law > Nonobviousness > Elements & Tests > General Overview***

[HN6] A known compound may suggest its homolog, analog, or isomer because such compounds often have similar properties, and therefore chemists of ordinary

skill would ordinarily contemplate making them to try to obtain compounds with improved properties. To find a prima facie case of unpatentability in such instances, a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention was also required.

***Patent Law > Nonobviousness > Elements & Tests > General Overview***

[HN7] Courts follow the standard statutory formulation under 35 U.S.C.S. § 103, which is whether the claimed subject matter would have been obvious at the time the invention was made.

***Patent Law > Nonobviousness > Elements & Tests > Predictability***

[HN8] When there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.

***Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof***

[HN9] One who claims a compound, per se, which is structurally similar to a prior art compound, must rebut the presumed expectation that the structurally similar compounds have similar properties.

***Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness***

[HN10] Generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.

***Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard***

[HN11] A person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art.

**COUNSEL:** David G. Conlin, Edwards Angell Palmer & Dodge LLP, of Boston, Massachusetts, argued for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola, of New York, New York. Of counsel on the brief was Mark Chao, Takeda Pharmaceuticals North America, Inc., of Lincolnshire, Illinois.

Kevin F. Murphy, Frommer Lawrence & Haug LLP, of New York, New York, argued for defendants-appellants. With him on the brief were Edgar H. Haug and Jeffrey A. Hovden.

**JUDGES:** Before LOURIE, BRYSON, and DYK, Circuit Judges. Opinion for the court filed by Circuit Judge LOURIE. Concurring opinion filed by Circuit Judge DYK. DYK, Circuit Judge, concurring.

#### OPINION BY: LOURIE

#### OPINION

[\*1352] LOURIE, *Circuit Judge*.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that *U.S. Patent 4,687,777* was not shown to be invalid under 35 U.S.C. § 103. *Takeda Chem. Indus., Ltd. v. Mylan Labs., 417 F. Supp. 2d 341 (S.D.N.Y. 2006)*. Because we conclude [\*\*2] that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

#### BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin--a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes--affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones [\*\*3] ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the

nucleus of the cell known as PPAR-gamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda, 417 F. Supp. 2d at 348-49*. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS (R), which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS (R) has enjoyed substantial commercial success since its launch in 1999. By [\*1353] 2003, it held 47% of the TZD market, and gross sales for that year exceeded \$ 1.7 billion. *Id. at 386*. The active ingredient in ACTOS (R) is the TZD compound pioglitazone, a compound claimed in the patent in suit.

Takeda owns *U.S. Patent 4,687,777* [\*\*4] (the "'777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:

[SEE DIAGRAM IN ORIGINAL]

or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:

[SEE DIAGRAM IN ORIGINAL]

or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

*Id.*, claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring. <sup>1</sup> That chemical structure, which has an ethyl substituent (C[2]H[5]) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, [\*\*5] *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda, 417 F. Supp. 2d at 360*. The formula



includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

[\*1354] Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

2. A compound as claimed in claim 1, wherein the compound is 5-4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:

[SEE DIAGRAM IN ORIGINAL]

1 Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." *Takeda*, 417 F. Supp. 2d at 351.

Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) *et seq.* to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), [\*6] asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH[3]) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:

[SEE DIAGRAM IN ORIGINAL]

Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103.

The court first [\*\*7] concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured through inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

## DISCUSSION

### A. Standard of Review

In this appeal, we are presented with one issue, namely, whether the asserted [\*1355] claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. [HN1] An invention is not patentable, *inter alia*, "if the differences between the subject matter sought to be patented and the prior art are [\*\*8] such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). [HN2] Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1238-39 (Fed. Cir. 2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

### B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply [\*\*9] a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that

such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's [\*\*10] remaining challenges to the district court's legal and factual rulings are simply without merit.

We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). The Court stated that [HN3] the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided [\*1356] by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

#### *I. Differences Between the Prior Art and the Claims*

##### *a. Selection of Compound b as Lead [\*\*11] Compound*

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the

closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that [HN4] "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Gra-biak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985).

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that [HN5] "[n]ormally a prima facie case of obviousness is based [\*\*12] upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* [HN6] A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Gra-biak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)).

That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.<sup>2</sup> While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness [\*\*13] inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine [\*\*1357] the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a

particular manner to establish prima facie obviousness of a new claimed compound.

2 We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that [HN7] the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether [\*\*14] the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.<sup>3</sup> Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [\*\*15] compound b as a lead compound.

3 The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's *U.S. Patent 4,287,200* (the "'200 patent'"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds." <sup>4</sup> *Takeda*, 417 F. Supp. 2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the

procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in [\*\*16] order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

4 Three divisional applications derive from the '200 patent. Those applications matured into *U.S. Patent 4,340,605*, *U.S. Patent 4,438,141*, and *U.S. Patent No. 4,444,779* (the "'779 Patent'"). The '779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F. Supp. 2d at 378.

[\*1358] The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. [\*\*17] Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not

have selected compound b as a lead compound for anti-diabetic treatment. Although [\*\*18] the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that [\*\*19] exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in [\*1359] the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find [\*\*20] such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time

Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious certain claims [\*\*21] covering a particular acid-addition salt, directly supports its position.

We disagree. The *KSR* Court recognized that[HN8] "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. [\*\*22] In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided [\*1360] "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to com-

pound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point [\*\*23] a compound with identified adverse effects." Thus, Pfizer does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. See *Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed. Cir. 2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

#### b. Choice of the Claimed Compounds

Even if Alphapharm had established that preliminary finding, and we have concluded that it did [\*\*24] not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F. Supp. 2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court [\*\*25] found nothing in the prior art to provide a

reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly [\*1361] from compound b in structure. *Id.* at 376 n.51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. [\*\*26] Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder*, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. [\*\*27] The court held that [HN9] "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the ho-

mologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that [HN10] generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of *Wilder*. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F. Supp. 2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds [\*\*28] in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda performed [\*1362] additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity [\*\*29] of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function

as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the [\*\*30] compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. [\*\*31] We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm [\*1363] failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.<sup>5</sup>

5 The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been [\*\*32] shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and

5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

## 2. Scope and Content of the Prior Art

Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 *patent* from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 *patent* prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 *patent* and the file history that appears in the court's opinion.

We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution [\*\*33] history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F. Supp. 2d at 378. In considering the prosecution history of the '779 *patent*, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n.59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed. Cir. 1986) ([HN11] "[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered [\*\*34] the prosecution history of the '779 *patent* in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

[\*1364] CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 *patent* have not been shown to have been obvious and hence invalid.

AFFIRMED

CONCUR BY: DYK

CONCUR

DYK, *Circuit Judge*, concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here--claim 2--is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of *U.S. Patent No. 4,867,777* ("'777 *patent*")--which are also referenced in the judgment--renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art *U.S. Patent No. 4,287,200* ("'200 *patent*"). Unfortunately our law concerning when a species [\*\*35] is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 301 F.2d 676, 683, 49 C.C.P.A. 993, 1962 Dec. Comm'r Pat. 232 (C.C.P.A. 1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant [\*\*36] must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 *patent*, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 *patent* also

generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 *patent*, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and

5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.